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Article

Development and Validation of a Stability-Indicating Gas Chromatographic Method for Quality Control of Residual Solvents in Blonanserin: A Novel Atypical Antipsychotic Agent

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Blonanserin is a novel atypical antipsychotic agent for the treatment of schizophrenia. Ethyl alcohol, isopropyl alcohol and toluene are utilized in the synthesis route of this bulk drug. A new validated gas chromatographic (GC) method for the simultaneous determination of residual solvents in blonanserin is described in this paper. Blonanserin was dissolved in *N*, *N*-dimethylformamide to make a sample solution that was directly injected into a DB-624 column. A postrun oven temperature at 240°C for approximately 2 h after the analysis cycle was performed to wash out blonanserin residue in the GC column. Quantitation was performed by external standard analyses and the validation was carried out according to International Conference on Harmonization validation guidelines Q2A and Q2B. The method was shown to be specific (no interference in the blank solution), linear (correlation coefficients $\geq$0.99998, $n = 10$), accurate (average recoveries between 94.1 and 101.7%), precise (intra-day and inter-day precision $\leq$2.6%), sensitive (limit of detection $\leq$0.2 ng, and limit of quantitation $\leq$0.7 ng), robust (small variations of carrier gas flow, initial oven temperature, temperature ramping rate, injector and detector temperatures did not significantly affect the system suitability test parameters and peak areas) and stable (reference standard and sample solutions were stable over 48 h). This extensively validated method is ready to be used for the quality control of blonanserin.

Introduction

Residual solvents (RSs) in drugs refer to the organic solvents that have been utilized but not completely removed during the manufacturing process of active pharmaceutical ingredients (APIs), excipients and drug products. Basically, there are three primary sources of RSs involved in the manufacturing process of API: synthetic materials or reagents, reaction by-products and reaction solvents by the introduction of synthetic materials. The length of synthetic route, the steps in which the solvents are being used, the impact of the organic solvents utilized in the follow-up steps on the solvents used previously, the purifying methods and the drying conditions of the intermediates, as well as the purification methods of the final products, are some key factors affecting the RS level in final products. The selection of organic solvents is crucial not only because these solvents play vital roles in reaction rate and yield of APIs (1), but also because they may influence crystal form, particle size and dissolution properties (2, 3).

International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use has been providing internationally recognized guidelines (4) on the determination of RS for many pharmacopoeias, such as the United States Pharmacopoeia (USP), British Pharmacopoeia (BP), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP) and Chinese Pharmacopoeia (CP). According to ICH Q3C, which gives comprehensive guidelines for RSs in drug substances, excipients and drug products, RSs are classified into four categories depending on the degree of toxicity and environmental hazard. The advantages of superior sensitivity, distinguished selectivity, high efficiency and short analysis cycle enable gas chromatography (GC) to be the most important tool to detect and analyze RS, which are primarily volatile compounds.

Blonanserin (AD-5423) is a novel atypical antipsychotic agent for the treatment of schizophrenia with high affinities to dopamine D2 and serotonin 5-HT2 A receptors (5, 6). Studies have indicated that the efficacy of blonanserin treatment for negative symptoms of schizophrenia was greater than placebo and haloperidol (7). Three organic solvents, namely, ethyl alcohol (EtOH), isopropyl alcohol (IPA) and toluene (PhMe), are used during the synthesis process of blonanserin. Based on ICH guidelines, EtOH and IPA are Class 3 solvents with the same maximum limit of 5,000 ppm. Additionally, inherently toxic PhMe belongs to Class 2 with a maximum limit of 890 ppm calculated on the basis of permitted daily exposure (PDE) of 8.9mg/day. Although many investigations have studied the analysis of a wide variety of RSs in APIs (8–11), excipients (12) and drug products (13), it is still essential to establish a validated GC method for determination of these three RSs exclusively in blonanserin. It is not only important for the quality control of this novel drug, but also critical as far as the imported drug registration is concerned in China.

The boiling points of EtOH, IPA and PhMe are 78, 82 and 111°C, respectively. Thus, a solvent with low boiling temperature, such as methanol (boiling point 64°), was not considered as an appropriate sample solvent because the tailing of solvent peak might interfere with the detection of EtOH and IPA. Water was also not selected because blonanserin has very low solubility ($<$100 μg/mL) in water. The use of a high boiling solvent to detect low boiling residual solvents have been widely applied and discussed (8, 10–11, 14), and this application is also recommended in USP and EP, especially for those water-insoluble samples. As a high boiling temperature solvent, *N*, *N*-dimethylformamide (DMF; boiling point 153°) was selected to be the sample solvent, because it dissolved the RSs and blonanserin very well, and showed no interference peaks.

Direct-injection and headspace (HS) sampling are basically the two most important sample introduction techniques for GC. Although the HS sampling method has become widely

used in recent years (15–18), direct-injection still possesses very competitive advantages and has been extensively applied (19), especially for regulatory criteria to control RS. This method is simple, economic and easy to operate, with short sampling and analysis cycle, and the repeatability of the results is normally higher than with the HS sampling method. Recently, Hattori *et al.* (20) published a GC–mass spectrometry (MS) method for the determination of blonanserin in human plasma that demonstrated that blonanserin is a semi-volatile compound. Thus, direct-injection would not lead to the accumulation of blonanserin in the GC column, as long as a postrun high oven temperature is performed to wash out the API.

This paper describes the development and validation of a precise, sensitive, accurate and robust gas chromatographic method for simultaneous determination of EtOH, IPA and PhMe in blonanserin bulk drug. The validated method was successfully applied to three different batches of this API.

Experimental

Materials

Blonanserin bulk drug (batch 1035, 1036 and 1037) was obtained from Dainippon Sumitomo Pharma Co (Chuo-ku, Osaka, Japan). EtOH (batch 200909311, purity 99.7%, Shanghai Zhenxing No. 1 Chemical Plant, Shanghai, China), IPA (batch 071201, purity 99.7%, Shanghai Lingfeng Chemical Reagent Co., Shanghai, China) and PhMe (batch 20090408, purity 99.5%, Sinopharm Chemical Reagent Co., Shanghai, China) were all of analytical reagent grade. HPLC/GC grade of DMF was provided by Merck (Darmstadt, Grmany).

Accurately weighed EtOH, IPA and PhMe were dissolved in DMF to make a stock reference standard mixture. The final concentrations of EtOH, IPA and PhMe were 1,190, 1,240 and 230 μg/mL, respectively.

Instrumentation and chromatographic conditions

An Agilent 6890 Series gas chromatographic system (Wilmington, DE) equipped with flame ionization detector (FID) was applied for the analysis. Separation for the RSs was performed on a DB-624 wide bore column, 30 m × 0.53 mm i.d., 3 μm film thickness (J&W Scientific, Folsom, CA). The GC parameters are summarized in Table I. A Sartorius CP224S analytical balance (precision 0.1 mg, Goettingen, Germany) was used for the weighing.

Table I
GC Parameters for the Method

Column	J&W Scientific DB-624, 30 m × 0.53 mm i.d., 3 μm film thickness
Carrier gas	Helium, 4.5 mL/min (constant flow)
Inlet temperature	210°C
Oven temperature	40°C (held 5 min) to 120°C at 10°C/min ramp, then to 220°C at 40°C/min ramp and held for 15 min
Postrun	Oven temperature at 240°C for 2 h at the end of the analysis procedure
Detector	FID, 250°C
Hydrogen flow	35 mL/min
Air flow	350 mL/min
Make-up gas	Helium, 25 mL/min
Injection volume	1 μL
Inlet split ratio	1:5

Sample preparation

Blonanserin (0.25 ± 0.001 g) was accurately weighed and transferred into a 10-mL volumetric flask. A quantity of DMF was added and hand shaking was performed to dissolve blonanserin. DMF was then added to volume, and the flask was shaken well to make a sample solution. DMF was regarded as the blank solution.

Validation procedure

The method was validated for specificity, linearity, accuracy, precision, detection limit, quantitation limit and robustness, in accordance with ICH Q2A and Q2B guidelines (21, 22).

Specificity was validated by comparing the retention times of individual RS peaks in reference standard solution and those in sample solutions. The blank solution should not interfere with the analysis in the GC method.

Ten concentration levels of linearity standard solution were prepared through the dilution of stock reference standard mixture. As a result, the linearity study was carried out from 1.19–1,190 μg/mL (equivalent to 47.6–47, 600 ppm) for EtOH, 1.24–1,240 μg/mL (equivalent to 49.6–49, 600 ppm) for IPA and 0.232–232 μg/mL (equivalent to 9.3–9, 280 ppm) for PhMe. Linear regression was conducted on the peak area of each RS (y) versus its calculated concentration (x, μg/mL). The correlation coefficient should be no less than 0.999 for each RS.

Recovery study was performed for the assessment of accuracy. Spiked samples were prepared by adding 0.5, 1.0 and 2.0 mL of stock reference standard mixture into accurately weighed (0.25 ± 0.001 g) blonanserin. A quantity of DMF was added before hand-shaking. After blonanserin was thoroughly dissolved, DMF was added to make a final volume of 10 mL. Triplicate preparations at each spiked concentration were made.

Intra-day and inter-day precision of the method were calculated as the relative standard deviations (RSDs) of the recovery test at each spiked concentration level. Acceptance criteria were set as follows: mean recovery should be between 90.0∼ 110.0%, and recovery RSDs should be no more than 5.0%.

Limit of detection (LOD) and limit of quantitation (LOQ) were calculated based on the following equations: $LOD = 3.3\sigma/s$ and $LOQ = 10\sigma/s$, where σ is the standard deviation of blank solution ($n = 20$), and s is the slope of linear curve with standard concentrations near the quantitation limit.

Robustness was studied on the variation of 10% on the carrier gas flow, 5°C on the initial oven temperature, 1°C/min on the temperature ramping rate and 10°C on injector and detector temperatures, as well as different columns and instruments. Retention time, number of theoretical plates and tailing factor of EtOH, as well as resolution factor between EtOH and IPA, were all used to evaluate the robustness. Additionally, solution stability was also evaluated by reinjecting reference standard solution and sample solution (batch 1035) within approximately two days.

External standard method was carried out to quantify the concentration of RSs in the sample solutions. Three concentration levels of linearity standard solutions [i.e., (i) 59.4 μg/mL,

(ii) 119 μg/mL and (iii) 238 μg/mL for EtOH] were selected to obtain the external standard correction factors (ESCFs). Triplicate injections were made at each concentration level, and the RSDs of the ESCFs should be less than 2.0 for each RS. The quantity of each RS in sample solutions could be obtained from the following equation:

$$Individual\ RS\ (ppm) = \frac{C_{sample}}{W_{sample}} \times 10 = \frac{A_{sample} \times AESCF}{W_{sample}} \times 10$$

where C_{sample} is the concentration of individual RS in sample solution (in μg/mL), W_{sample} is the weight of sample (in g), A_{sample} is the peak area of each RS in the sample, AESCF is average external standard correction factor for individual RS, and 10 stands for dilution factor.

Results and Discussion

Selection of solvent for sample preparation

The selection of sample solvent was based on two facts: (i) the RSs determined in this paper all had low to medium boiling temperature; (ii) blonanserin is insoluble in water. To avoid the possible interference of low boiling temperature with RSs, some organic solvents with higher boiling temperatures were investigated. Three common solvents for RS determination, namely, DMF, *N*, *N*-dimethyl acetamide (DMAc) and dimethyl sulfoxide (DMSO), were chosen for the optimization. Results showed that all of the three solvents could reach a solubility of 25 mg/mL for blonanserin. However, some tiny interference peaks might appear close to the elution time of EtOH when using DMAc or DMSO as a blank solution. In contrast, the blank chromatogram of DMF showed no interfering peaks within the retention time windows of all three RSs.

Selection of chromatographic conditions

Because the target RSs are of different polarities (i.e., low polarity for PhMe and high polarity for EtOH and IPA), a variety of GC columns of different stationary phases were selected. Peak retention time, number of theoretical plates, tailing factor and resolution factor were considered to be the most important system suitability factors to select the column. After repeated comparisons and experiments, the medium polarity DB-624 column (6% cyanopropylphenyl–94% dimethylsiloxane) was shown to have the optimal parameters for these factors. Moreover, a programmed oven temperature was set to obtain a shorter analysis cycle and even sharper peak of PhMe without impairing its separation with adjacent peaks.

Preliminary tests for appropriate inlet split ratio (1:10, 1:5 and 1:2) were further conducted. Although decreasing the inlet split ratio could substantially increase the amount of RS injected into the column, thus theoretically raising the sensitivity, it might also cause peak broadening or tailing, which would dampen the sensitivity. According to our data, the tailing factors of EtOH, IPA and PhMe were 5.6, 1.9 and 2.6 under the split ratio of 1:2. Nevertheless, much lower tailing factors were obtained under the optimum split ratio of 1:5.

Over a 100-time concentration span, the RSs had consistent peak retention times. At a 95% confidence level, the peak retention time intervals of EtOH, IPA and PhMe were 3.729–3.899, 4.637–4.805 and 11.508–11.532 min, respectively (n = 15). Reference standard solution containing 119 μg/mL (equivalent to 4,760 ppm) of EtOH, 124 μg/mL (equivalent to 4,960 ppm) of IPA and 23.2 μg/mL (equivalent to 928 ppm) of PhMe, respectively, was utilized as a system suitability test solution to evaluate the column performance parameters. The system suitability test data are summarized in Table II. Figure 1 shows the GC chromatograms of a typical blank solution, reference standard solution and sample solution under the selected method conditions.

Analytical method validation

The chromatographic method described previously was used to analyze blonanserin samples. The results for method validation are described as follows.

Specificity

The retention times of the eluted RSs in blonanserin samples as well as spiked samples were all within their respective time intervals at 95% confidence level. Furthermore, the blank solution (DMF) did not elute any peaks within the time intervals. Therefore, the specificity of this method was validated.

Table II
Summary of the System Suitability Test Data of the GC Method

Residual solvent	Ethyl alcohol	Isopropyl alcohol	Toluene
Retention time (min)	3.814	4.738	11.520
Number of theoretical plates	19,526	16,802	243,119
Tailing factor	1.6	1.2	1.0
Resolution	7.29	57.4	

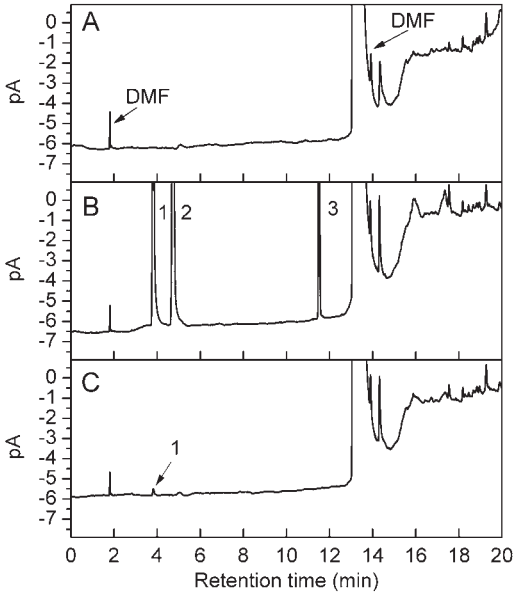

Figure 1. GC–FID chromatograms of blank solution (A); reference standard solution containing 119 μg/mL of ethyl alcohol, 124 μg/mL of isopropyl alcohol and 23.2 μg/mL of toluene (B); and sample solution (C). Peaks 1, 2 and 3 refer to residual ethyl alcohol, isopropyl alcohol and toluene, respectively.

Linearity

Table III shows the linearity parameters of each RS. The linear regression results showed good correlation ($r \geq 0.99998$, $n = 10$) between peak area of individual RS (y) versus concentrations (x, μg/mL). The highest concentration for each RS was 100 times greater than the lowest one.

Accuracy and precision

To assess accuracy, three concentration levels of standard solutions were added into blonanserin sample to prepare recovery test solutions. With EtOH as an example, the spiked concentration was approximately 2,380, 4,760, and 9,520 ppm, respectively, corresponding to 50, 100 and 200% of the maximum limit of EtOH according to ICH guidelines. The mean recoveries for EtOH, IPA and PhMe were between 96.6–101.7, 94.1–101.4 and 98.1–102.1%, respectively, and the RSDs were between 0.2 and 1.6% ($n = 6$).

Table III
Summary of Linear Regression Analysis of Ethyl Alcohol, Isopropyl Alcohol and Toluene using 10 Levels of Concentration of the GC Method*

Residual solvent	Equation	Concentration range (μg/mL)	Range (ppm)	Correlation coefficient (r)
Ethyl alcohol	$y = 1.259x - 3.073$	1.19–1,190	47.6–47,600	0.99998 (n = 10)
Isopropyl alcohol	$y = 1.325x - 2.882$	1.24–1,240	49.6–49,600	0.99999 (n = 10)
Toluene	$y = 2.925x - 0.703$	0.23–232	9.3–9,280	0.99998 (n = 10)

*Note: x stands for concentration of each residual solvent and y stands for peak area.

Table IV
Summary of Accuracy and Precision Results of the GC Method

Residual solvent	Spiked (mg/g)	Recovery (%)	Intra-day (n = 3) precision (%)	Inter-day precision (n = 3 days, three replicates per day) (%)
Ethyl alcohol	2.38	96.6	1.6	2.6
	4.76	99.0	0.9	1.2
	9.52	101.7	0.7	1.2
Isopropyl alcohol	2.48	94.1	1.5	2.0
	4.96	99.7	0.2	2.1
	9.92	101.4	0.2	1.5
Toluene	0.46	98.1	0.9	1.6
	0.93	98.4	1.0	0.6
	1.85	101.2	1.2	1.0

To evaluate the precision of the method, intra-day and inter-day reproducibility of the recovery experiments were conducted. The inter-day precision was evaluated over three successive days at each spiked concentration level. Table IV summarizes the intra-day and inter-day recoveries and RSDs. The mean recoveries of low, medium and high levels were all within 94.1 and 101.7% for each RS, and the RSDs for the mean recoveries were between 0.6 and 2.6%. The validation data guaranteed the accuracy and precision of the GC method.

LOD and LOQ

LOD and LOQ of each RS were calculated based on the standard deviation of the response and slope. Four concentration levels close to quantitation limit were selected and each level was injected thrice to get the slope of linear curve. According to calculation results, the LODs were 0.2, 0.2 and 0.1 ng ($n = 12$) for EtOH, IPA and PhMe (corresponding to 8, 8 and 4 ppm), respectively, and the accordingly the LOQs were 0.7, 0.6 and 0.3 ng (corresponding to 28, 24 and 12 ppm) ($n = 12$).

Robustness

This method was robust to the small variations in GC conditions, i.e., carrier gas flow from 4.0 to 5.0 mL/min, initial oven temperature from 35 to 45°C, temperature ramping rate from 9 to 11°C/min, injector temperature from 200 to 220°C, and detector temperature from 240 to 260°C. The retention time, number of theoretical plates and tailing factor of each RS, and the resolution factor between adjacent RSs were met for all the variations (Table V). Variations of the peak areas of each RS in system suitability test solution were all between 96 and 104% of the peak areas obtained from the method condition. Moreover, the retention times of each RS from another column and instrument were all within ±1 min of the retention times obtained from the primary column and instrument.

Real sample analysis

The external standard method was applied for real sample determination. The AESCFs for EtOH, IPA and PhMe were 0.83266, 0.78416 and 0.35321, with RSDs of 1.7, 1.6 and 1.0% ($n = 9$), respectively. EtOH was the only RS detected in the samples, with the peak retention times all within 95% confidence interval by replicate injections of sample solutions. The quantity of EtOH residue in blonanserin was determined to be

Table V
Summary of the System Suitability Parameters on the Changes of GC Conditions

Different instruments	Different batch of columns	Flow ± 10% (mL/min)	Initial T ± 5 (°C)	T rate ± 1°C (°C/min)	Injector (°C)	Detector (°C)	Retention time (min) EtOH	Number of theoretical plates EtOH	Tailing factor EtOH	Resolution factor EtOH/IPA
GC A	Batch A	4.5	40	10	210	250	3.814	19526	1.6	7.29
GC B	Batch B	4.5	40	10	210	250	3.575	12973	1.8	6.17
GC A	Batch A	4.0	40	10	210	250	4.283	20343	1.6	7.71
GC A	Batch A	5.0	40	10	210	250	3.441	17601	1.6	6.94
GC A	Batch A	4.5	35	9	210	250	4.232	21801	1.6	8.65
GC A	Batch A	4.5	45	11	210	250	3.467	21378	1.5	6.83
GC A	Batch A	4.5	40	10	200	240	3.807	18063	1.6	7.12
GC A	Batch A	4.5	40	10	220	260	3.805	17346	1.6	7.43

58 ppm (batch 1035), 54 ppm (batch 1036) and 56 ppm (batch 1037), respectively. Replicate tests were performed on the analyses of batch 1037, and the RSD of the quantification results was 7.7% ($n = 6$).

The bulk drug substance of blonanserin has a 3-step synthesis route, in which PhMe is used in all the three steps, whereas IPA is only utilized in the second step. However, EtOH was the only RS detected in the real samples because it is used as the solvent for recrystallization in the last step, after which no organic solvent is further utilized. PhMe and IPA residues in the bulk drug substance may be fully washed out by the repeated recrystallization processes, which is why they were not detected in the real samples.

Stability of reference standard and sample solutions

The system suitability test solution was re-injected at the time points of 0, 5.5, 10, 15, 23, 38 and 53 h to investigate stability. Results suggested that the RSDs of peak areas were 0.7, 1.7 and 0.9% ($n = 7$) for EtOH, IPA and PhMe, respectively, indicating that the reference standard solution was stable over 53 h.

The injection of sample solution (batch 1035) was also repeated at the time points of 0, 5, 13, 28, 43 and 48 h. The RSD of the detected EtOH peak areas in the sample solution was 8.9% ($n = 6$).

The GC chromatograms obtained by the stability tests also revealed that the peak retention times of individual RS in reference standard solution and sample solutions over a 2-day period were all within their respective 95% confidence intervals, and the number of theoretical plates and tailing factors of the peaks did not change significantly. The results suggested that multiple direct injections on the column in the GC method did not show any significant disturbance on system suitability parameters of the RS peaks.

Preliminary tests have been made to determine the fate of blonanserin in the DB-624GC column. Although no peaks except EtOH and DMF were eluted when the oven temperature was set at 220°C, a big peak eluted at 94 min when the oven was set at 240°C, while it eluted at 67 min when the oven was set at 250°C. A GC–MS method was performed to verify whether blonanserin would be decomposed in the column. GC–MS was performed on a 7890A GC system coupled to a 7000A triple quadrupole mass spectrometer (Agilent, Santa Clara, CA). A medium polar HP-1701MS fused-silica capillary column, 30 m × 0.25 mm i.d., 0.25 μm film thickness (J&W Scientific, Folsom, CA) was used. Carrier gas was helium at a flow rate of 0.8 mL/min because this rate reached the average velocity of 32 cm/s for the carrier gas, which was very close to the average velocity for the carrier gas in the DB-624 column in the method conditions. The oven temperature began at 40°C (held 5 min), then was raised to 120°C at a 10°C/min ramp, then was raised to 240°C at a 40°C/min ramp and held for 120 min. The injector temperature was set at 210°C, and the transfer line temperature was set at 250°C. Split ratio was set at 1:5. Ionization energy of 70 eV was set for electron impact (EI) mode. The ion source temperature was set at 230°C. Full scan mode from m/z 50 to 500 was performed. To avoid solvent contamination, methanol was used as the sample solvent to make a sample solution of blonanserin (0.25 mg/mL) and the solvent

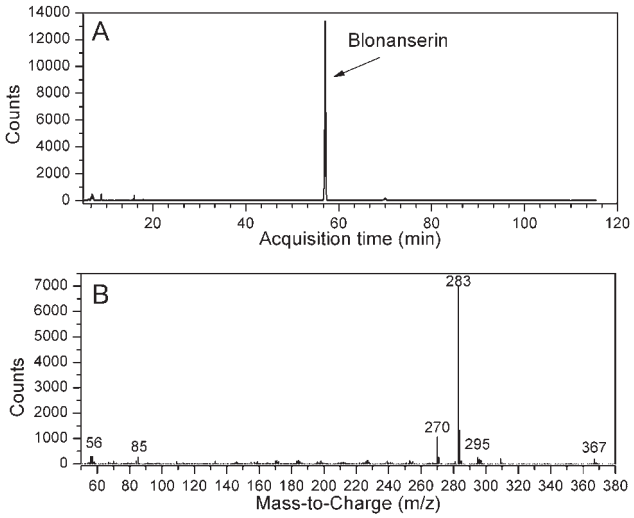

Figure 2. GC–MS TIC chromatogram of blonanserin solution in methanol (25 mg/mL) (A); and EI mass spectrum of blonanserin (B). GC–MS conditions: HP-1701MS fused-silica capillary column (30 m × 0.25 mm, 0.25 μm); helium flow rate, 0.8 mL/min; oven temperature, 40°C (held 5 min) to 120°C at 10°C/min ramp, then to 240°C at 40°C/min ramp and held for 120 min; injector temperature, 210°C; transfer line temperature, 250°C; split ratio, 1:5; EI mode ionization energy, 70 eV; ion source temperature, 230°C; full scan mode, m/z 50 to 500.

delay was set at 4.0 min to cut off the methanol peak. As a result, the TIC chromatogram (Figure 2A) obtained had only one major peak with a retention time approximately 57 min, which was equivalent to 41 min after the oven reached 240°C. The full scan spectrum (Figure 2B) of the peak matched the literature (20) very well, which confirmed that the peak was blonanserin but not its decomposition. No decomposition peak was detected when the oven temperature was set at 300°C, demonstrating that blonanserin is stable under such a high temperature.

Because blonanserin will be washed out of the GC column if the oven temperature is set at 240°C or higher, an appropriate postrun procedure should be appended to the method. However, a high-temperature column cleaning procedure after each injection was unnecessary, because blonanserin residue in the GC column exhibited no interference with the number of theoretical plates and tailing factors of the RS peaks. Moreover, the testing results of the sample solutions over two days showed no significant difference, which also indicated the stability of this method. A postrun oven temperature at 240°C for approximately 2 h at the end of the analysis procedure has been demonstrated to be the easy way to wash blonanserin from the column without prolonging each analysis cycle. The system suitability test solution was injected again after the postrun, and results showed that the retention time, tailing factor and peak area for each RS did not change significantly, which demonstrated that the column was ready to be reused without any contamination.

The HS sampling method has the merits of avoiding injector and column contamination and matrix effects, and prolonging the lifetime of a GC column. However, as far as blonanserin is concerned, the validated direct-injection GC method is thought to be suitable, feasible and cost-effective, especially concerning the multi-batch quality control during the manufacturing.

Conclusion

The purpose of this study was to develop a validated gas chromatographic method for quantitating residual ethyl alcohol, isopropyl alcohol and toluene in blonanserin. This method was demonstrated to be specific, linear, sensitive, accurate, precise and robust. The easily operated and cost-effective direct-injection method proved to have no column contamination and matrix effects. Three batches of blonanserin bulk drug were selected for the real sample analysis, and the results indicated that ethyl alcohol was the only RS detected in this bulk API. Although the concentration of residual ethyl alcohol was very low (50–60 ppm), it was still detectable due to low LOD (8 ppm) and LOQ (28 ppm) of this method, and the quantitating results were repeatable. However, in accordance with ICH criteria, the presence of such a trace level of ethyl alcohol in API is acceptable and will not cause any damage to human health.

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